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CONTRACT NO: DAMD17-90-C-0070

TITLE: PROTEINS OF HUMAN IMMUNODEFICIENCY VIRUS THAT  
CROSS-REACT WITH HUMAN "SELF" ANTIGENS

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REPORT DATE: August 20, 1993

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and  
Development Command, Fort Detrick  
Frederick, Maryland 21702-5012

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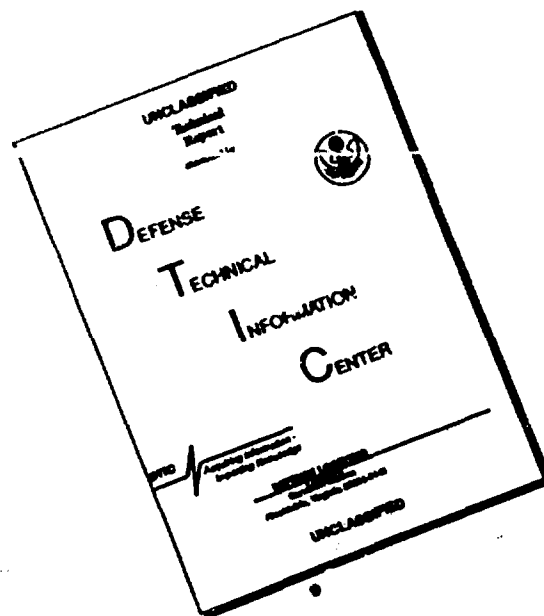
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1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE 20 August 1993	3. REPORT TYPE AND DATES COVERED Final Report (5/21/90 - 7/20/93)		
4. TITLE AND SUBTITLE Proteins of Human Immunodeficiency Virus that Cross-React with Human "Self" Antigens		5. FUNDING NUMBERS Contract No. DAMD17-90-C-0070		
6. AUTHOR(S) Michael B.A. Oldstone, M.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Scripps Clinic Research Institute 10666 North Torrey Pines Road La Jolla, California 92037		8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research & Development Command Fort Detrick Frederick, Maryland 21702-5012		10. SPONSORING / MONITORING AGENCY REPORT NUMBER		
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited		12b. DISTRIBUTION CODE		
13. ABSTRACT (Maximum 200 words) HIV causes a persistent infection that results in AIDS, a major health to military and civilian populations we have and continue to study both arms of the immune system -- one that produces antibodies and one that makes cytotoxic T lymphocytes (CTL). Our purpose is two-fold. First, to determine which is important, or more essential, in producing immunity. This data should be essential for vaccine production to that end we have evaluated CTL activity in selected patients from the onset of HIV infection and through their clinical course. Second, to determine the role of antibody and/or CTL in contributing the disease. Toward that end we have defined, in three separate HIV-1 infected individuals, monoclonal antibodies that react with gp41 aa644-663, but also binds to a novel antigenic determinant on mammalian astrocytes.				
14. SUBJECT TERMS Cytotoxin T Lymphocyte; molecular mimicry; cross-reactive determinants; HIV; AIDS; Biotechnology; Vaccines; RAD I; Humans; Lab Animals			15. NUMBER OF PAGES	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

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## TABLE OF CONTENTS

	<u>Page Number</u>
Front Cover	1
Report Documentation Page	2
Foreword	3
Table of Contents	4
Final Scientific Report: Introduction, Body, Conclusions	5-14
Publications	14-16
Personnel	16

**Final Scientific Report**  
**Army Contract Number DAMD17-90-C-0070**  
**Principal Investigator: Michael B. A. Oldstone, M.D.**

**I. Introduction/Overview**

The molecular anatomy of the HIV-1 genome and its replicative strategy is well known. By contrast how the virus causes disease is poorly understood. Similarly, which of the two arms of the immune system -- the one that produces antibodies or the one that generates cytotoxic T lymphocytes (CTL) -- is more important in producing vaccine induced immunity, is not clear. In addition to their protective role, antibodies and CTL also contribute to disease in several viral infections. To that end, we studied in selected HIV-1 patients the generation of monoclonal antibodies to HIV-1 gp41 that also bound to mammalian astrocytes. Using competitive inhibition assay we noted that all three monoclonal antibodies studied bound to gp41 amino acid (aa) sequence 644-663. These results record molecular mimicry between a novel astrocyte antigen and a gp41 structural protein. Further, they document that an antibody response generated in some HIV-1 infected individuals is able to bind to self antigen or astrocytes. Additionally, we analyzed CTL in HIV-1 infected individuals. In four individual patients we charted the generation of CTL from the onset of infection, prior to the generation of neutralizing antibodies, during the course of their infection. The highest CTL response was to envelope (ENV) with responses to GAG, POL, and NEF occurring later during the course of infection. CTL ENV response was associated with the decrease in viral load during the initial phase of viral infection. In two patients, a decrease in CTL response occurred several months later. The correlation of this diminished response with enhanced viral load and antibody titers to the patient's viral isolate is currently under study.

The first half of support (Mid-Term Report) continued our studies to define and fine map the immunodominant domain of HIV-1 and HIV-2 for B cell (antibody) responses. Utilizing synthesized peptides and several raised murine monoclonal antibodies, the minimal essential epitope was found to consist of 7 aa peptide: aa603-609, HIV-1; aa597-603, HIV-2 -- both containing flanking cysteine residues. Thus, during the first half of support we documented the essential contribution of the flanking cysteines and solved the two-dimensional structure of this B cell epitope using NMR. Of murine monoclonal antibodies raised to HIV-1 gp41 aa598-609, a few (7 of 51) also reacted with a novel astrocyte antigen. Conditions in which this novel antigen was expressed and the topographic areas in the brain where the greatest expression occurred was determined. Three expression libraries were constructed, but despite screening  $\sim 6 \times 10^6$  plaques from each library, we were unable to enhance for and isolate the gene that encoded the novel astrocyte antigen mimicking HIV-1 gp41 segment. CTL responses to HIV were undertaken and two novel CTL epitopes mapped. Further, conditions for analyzing peripheral blood mononuclear samples harvested and to be harvested for CTL activity, from the six patients being evaluated from onset of disease until AIDS, were established.

**II. Specific Accomplishments**

a) Molecular Mimicry Accompanying HIV-1 Infection -- Human Monoclonal Antibodies that Bind to GP41 and to Astrocytes

Nine human monoclonal antibodies that reacted with HIV-1 gp160 were obtained and studied. Three monoclonal antibodies from three different individuals were found to bind to HIV-1 gp41 and also cross-reacted with mammalian astrocytes. (Table 1).

Table I  
Monoclonal Antibodies Raised During HIV-I Infection  
that Bind to HIV-1 gp41 but also Cross-React with Astrocytes

Monoclonal Antibody	Source	Species	Characteristics	Binds to (protein)	HIV Reactivity to gp41 Sequence	Cross-React with Reactive Astrocytes
M22*	MBAO	Mouse	Raised by immunization with peptie, IgG1 Ab	gp41	aa603-609	+ + +
15G1	ND	Human	Raised during infection, IgG2 Ab	gp41	aa644-663	+ + +
98-6	SZ	Human	Ibid, IgG2 Ab	gp41	aa644-663	+ +
167-7	SZ	Human	Ibid, IgG1 Ab	gp41	aa644-663	+
50-69 120-16 126-6 181-D 246-D	SZ	Human	Ibid, IgG Ab	gp41	Not to aa644-663 or aa603-609	NIL
MT-B22	ND	Human	Ibid, IgG Ab	gp120	NIL	NIL

\*One of several murine and rat antibodies that bind to both HIV-1 gp41 and astrocytes.

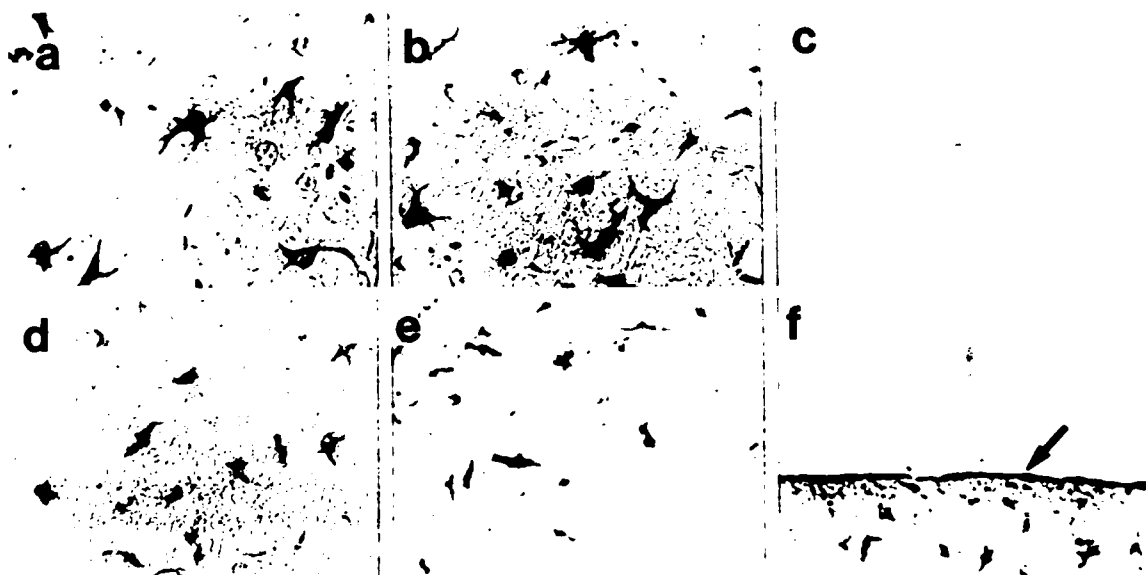


Figure 1

**Figure 1** shows staining of reactive astrocytes in brain sections from scrapie-infected mice by cross-reactive anti-HIV-1 gp41 antibodies. Strong staining was seen with ND-15G1 and weaker staining with SZ-98.6 and SZ-167.7. Mouse mAb M22 was used as a positive control, and SZ-120.16, which did not stain reactive astrocytes, was a negative control. The *glia limitans* (arrow) was consistently stained by the cross-reactive antibodies (f). Key: a, mouse monoclonal M22; b, hu mAb ND-15G1; c, hu mAb SZ-120.16; d & f, hu mAb SZ-98.6; and e, hu mAb SZ-167.7.

Mapping of these three monoclonal antibodies' specificity using HIV-1 gp41 peptides located their epitopes to aa644-663 and established their conformation dependence.

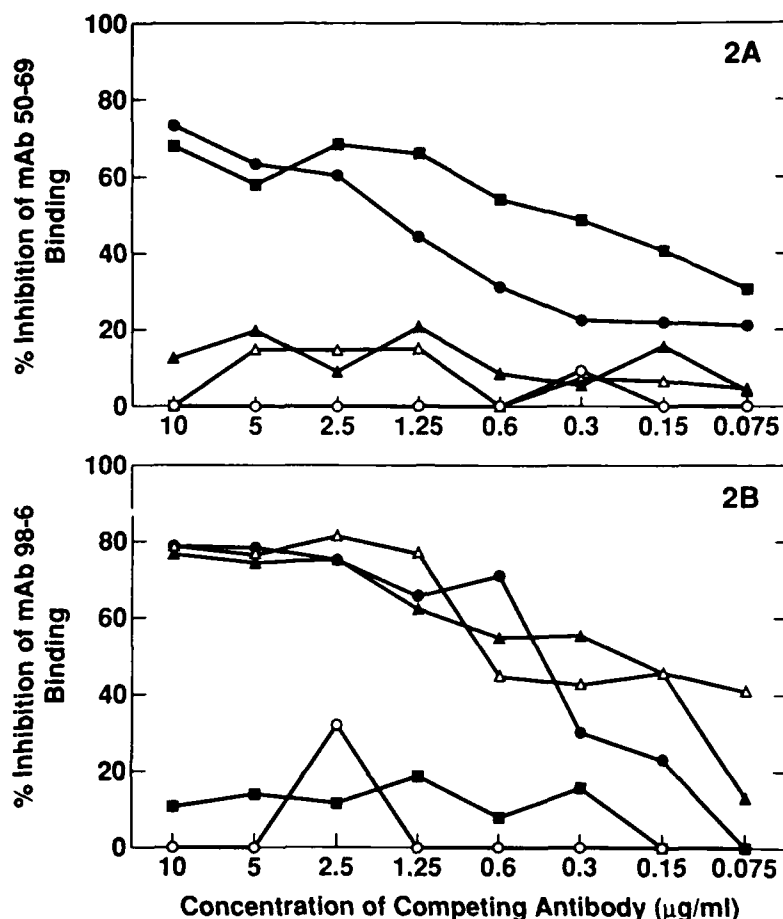


Figure 2A & 2B

**Figure 2A & 2B** shows the competition assays for inhibition of binding of human mAbs to whole HIV-1 lysate. Key: SZ-50.69, SZ-98.6, ND-15G1, HIV<sup>+</sup> serum, control serum.

**A)** ND-15G1 did not inhibit the binding of the immunodominant region 1-reactive mAb SZ-50.69 to HIV lysates. In contrast, both HIV<sup>+</sup> serum and SZ-50.69 itself effectively competed with labeled SZ-50.69.

**B)** ND-15G1 inhibited the binding of the immunodominant region 2-reactive mAb SZ-98.6 to HIV lysates. HIV<sup>+</sup> serum and the mAb SZ-98.6 also competed with the labeled antibody, but neither SZ-50.69 nor control HIV<sup>-</sup> serum inhibited SZ-98.6 binding.

The six other human monoclonal antibodies to HIV-1 (Table 1) bound to gp41 or gp120 but not to reactive astrocytes in brain tissue.



The sharing of linear or conformational protein determinants is termed molecular mimicry (see M.B.A. Oldstone, Molecular Mimicry and Disease. *Cell* 50:819-820, 1987). The consequences of such mimicry by antibodies to HIV interacting with astrocytes may play a role in the dementia of AIDS patients since a major function of astrocytes is to maintain the appropriate milieu for neuronal function. The finding of such cross-reactive antibodies adds to the evidence of a possible autoimmune pathogenesis for some of the disease manifestations accompanying HIV infection. For anti-astrocyte antibodies to disturb CNS function they must be present within the brain parenchyma during disease. This could occur via the extravasation of antibodies directly from serum into the brain and/or the intrathecal production of antibodies by B cells present within the CNS. Reactive astrogliosis is an early consequence of HIV infection of the CNS, occurring prior to clinical manifestation of disease. We noted that astrocyte expression of the cross-reactive epitope was widespread in the CNS during astrogliosis, particularly on endfeet forming the *glia limitans*. Astrocytes' endfeet are in intimate contact with blood vessels and would come into contact with extravasating antibody.

b) Attempts to Isolate the Astrocyte Gene that Encodes the 43kD Astrocytic Protein that Binds to Monoclonal Antibodies Raised Against the HIV-1 GP41 Immunodominant Domain and Studies of Tissue Factor (TF) in Astrocytes

Three libraries were constructed that had high expression of the 43kD astrocytic protein. One library was created from brains of mice infected with Theiler's virus, a second from brains of mice infected with scrapie agent and a third from scrapie-infected mouse hippocampus. Although several suggestive positive colonies were detected using mouse antibodies to HIV-1 gp41, none enriched or amplified. Approximately  $5 \times 10^6$  plaques were screened from each library. While concurrently we could select and amplify out other astrocyte specific genes, i.e., the gene encoding for glial fibrillary acidic protein, we were unsuccessful in obtaining the gene encoding the novel astrocyte 43kD protein.

However, while studying and manipulating astrocytes for the above cloning studies we serendipitously noted that astrocytes are the primary source of TF in the CNS. Analysis of murine brain sections by *in situ* hybridization demonstrated high levels of TF mRNA in cells that expressed glial fibrillary acidic protein.

For Figure 3 -- See next page

**Figure 3** shows that TF mRNA is expressed in astrocytes. Three  $\mu$ m thick scrapie-infected mouse brain sections were sequentially hybridized with a  $^{35}$ S-labeled anti-sense mouse TF riboprobes and then reacted with polyclonal anti-GFAP antibodies to identify astrocytes. TF mRNA-positive cells expressed GFAP (A-D) indicating that they were astrocytes. The GFAP positive *glia limitans* lining the brain (arrow, E,F) is negative for TF mRNA expression because of the lack of astrocyte cell bodies in this limiting boundary. In contrast, the overlying *arachnoid mater* (arrowhead, E,F) is strongly positive. Positive hybridization signals appear as black grains (A,C,E,F) or as blue-green grains using polarized light epiluminescence (B,D). The brown precipitate identifies astrocyte cell bodies and structures containing GFAP. Magnification is either  $\times 400$  (A,B,E) or  $\times 1000$  (C,D,F).

In addition, primary astrocyte cultures and astrocyte cell lines from mouse, rat and human constitutively express TF mRNA and functional protein.

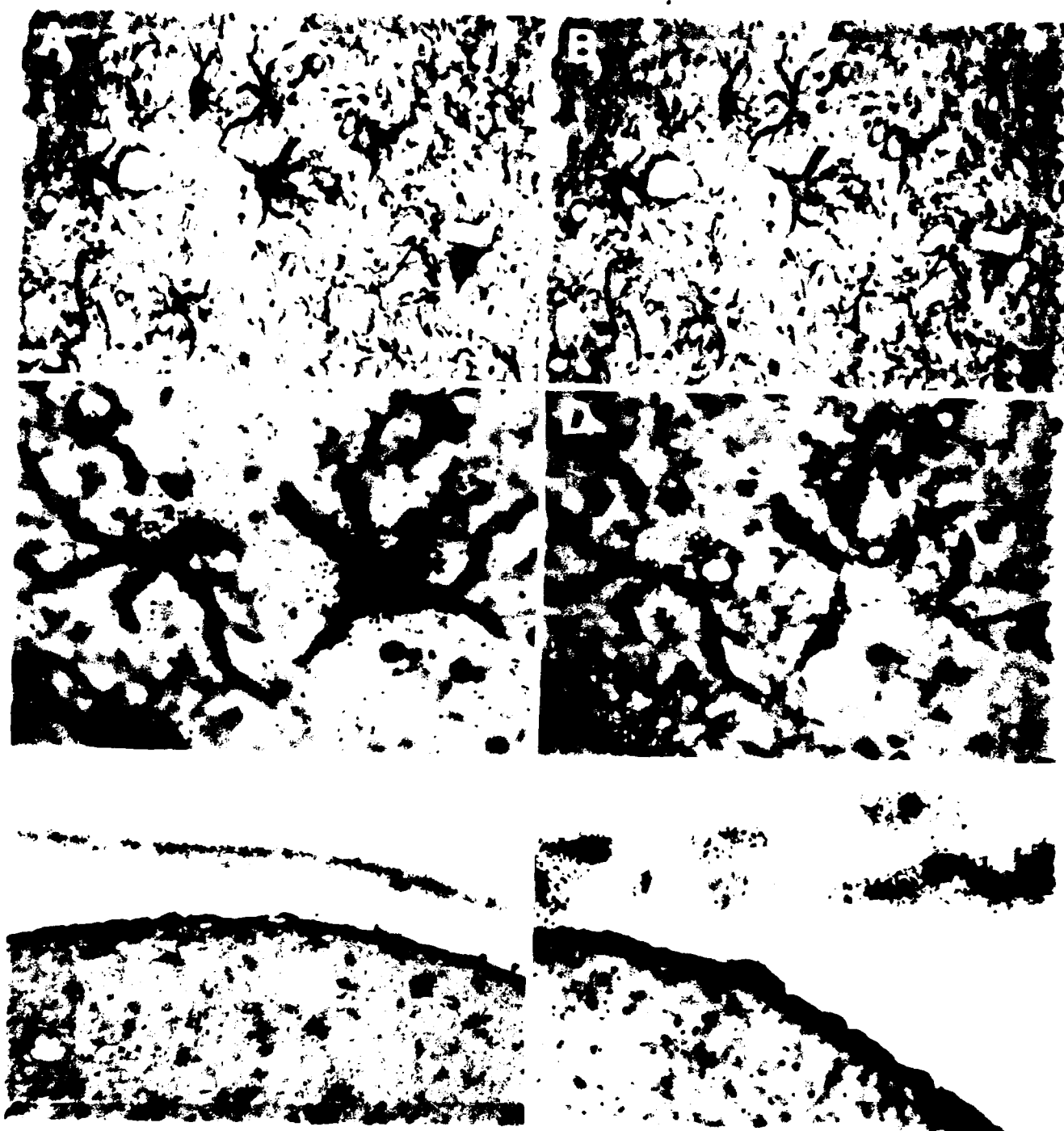


Figure 3

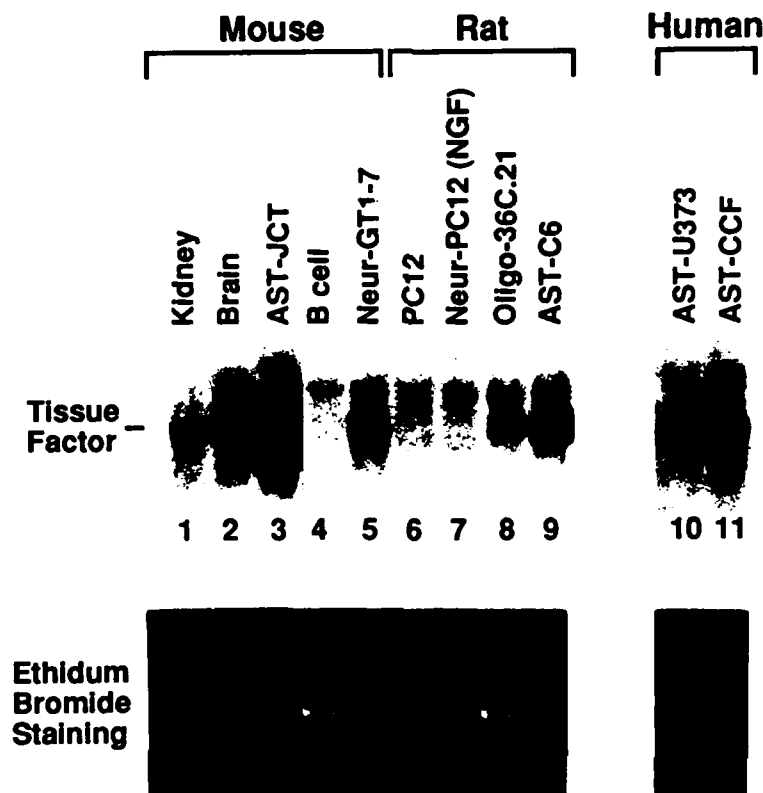


Figure 4

**Figure 4** shows TF is expressed in astrocyte cell lines of various species. Total RNA was isolated from mouse kidney and brain, the murine astrocyte cell line JCT, the rat glioma cell line C6, two human astrocytic cell lines U373 MG and CCF-STTG1, the rat oligodendrocyte cell line 36C.21, the mouse neuronal cell line GT1-7, rat PC12 cells both undifferentiated, and differentiated with  $\beta$ NGF, and as a negative control the BALB/c mouse myeloma B cell line J558L. Ten  $\mu$ g of each RNA was resolved on a formaldehyde denaturing gel, transferred to a nylon membrane and hybridized sequentially to  $^{32}$ P-labeled murine and human TF cDNA probes. This was required because under the stringent conditions used the mouse TF probe did not cross-hybridize with the human TF mRNA. The membrane was washed at high stringency (0.2x SSC, 60°C) and exposed overnight to autoradiography. Various housekeeping genes utilized (GAPDH, CHO-B &  $\beta$ -actin) all varied in their expression between the different cell lines and species. Therefore, the original ethidium bromide staining of the gel was used to indicate RNA loading.

c) Analysis of CTL Activity in HIV-1 Infected Individuals

We established procedures to recover active CTL from peripheral blood mononuclear cells (PBMM) collected several years earlier and stored in liquid nitrogen. Figure 5 shows a typical CTL assay. Panel A is the data on MHC-restricted targets, Panel B on allogeneic targets, and Panel C for NK cell activity. Observe Panel A and note high CTL response to ENV over a wide-dose response, significant response to GAG, negligible response to NEF and TAT. Note the controls of uninfected cells (uninf) and vaccinia virus recombinant expressing  $\beta$ -galactosidase ( $\beta$ -GAL). Note in Panel B the absence of response in allogeneic cells infected with vaccinia virus expressing ENV or GAG with the patient's same CTL and assay run at the same time.

EXAMPLE OF DATA FROM A TYPICAL CTL ASSAY

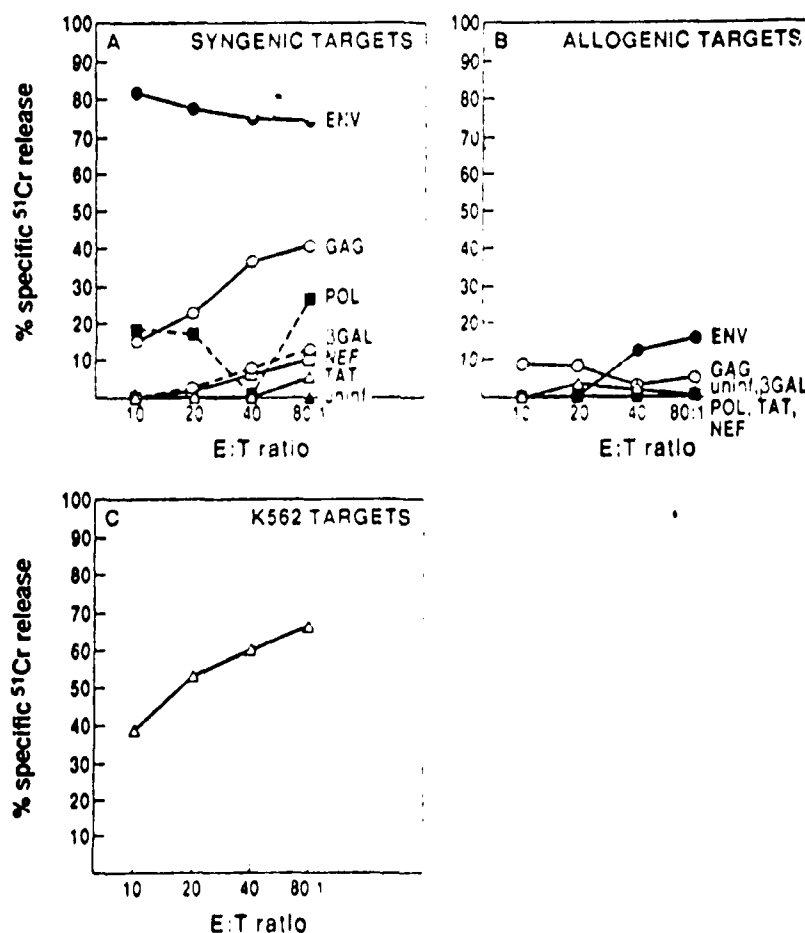


FIGURE 5

CTL activity was HLA Class 1 restricted and dependent on CD8<sup>+</sup> cells as determined by 1) use of HLA Class 1 transfected cells and 2) CD4 and CD8 antibody depletion studies.

Four patients, SUMA, INME, WEAU and BORI were studied using the format shown in Figure 6 along the patient's own B cells transformed with EBV and infected with vaccinia virus expressing either HIV-1 envelope (ENV), GAG, polymerase (POL), NEF or beta galactosidase (negative control). In addition, a number of peptides were synthesized (see Figure 6) and used to coat uninfected target cells.

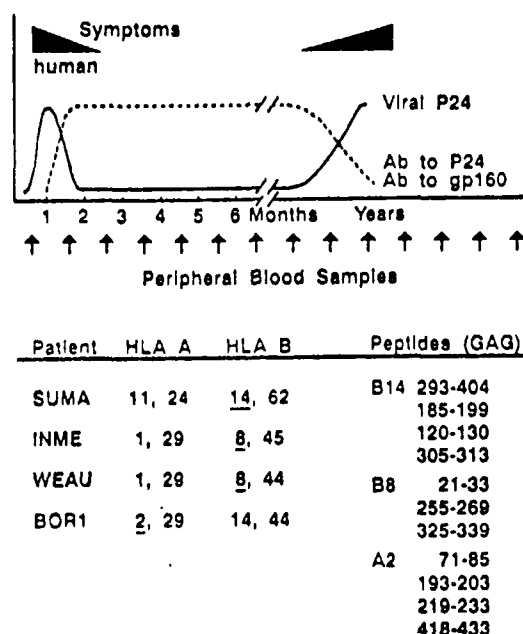


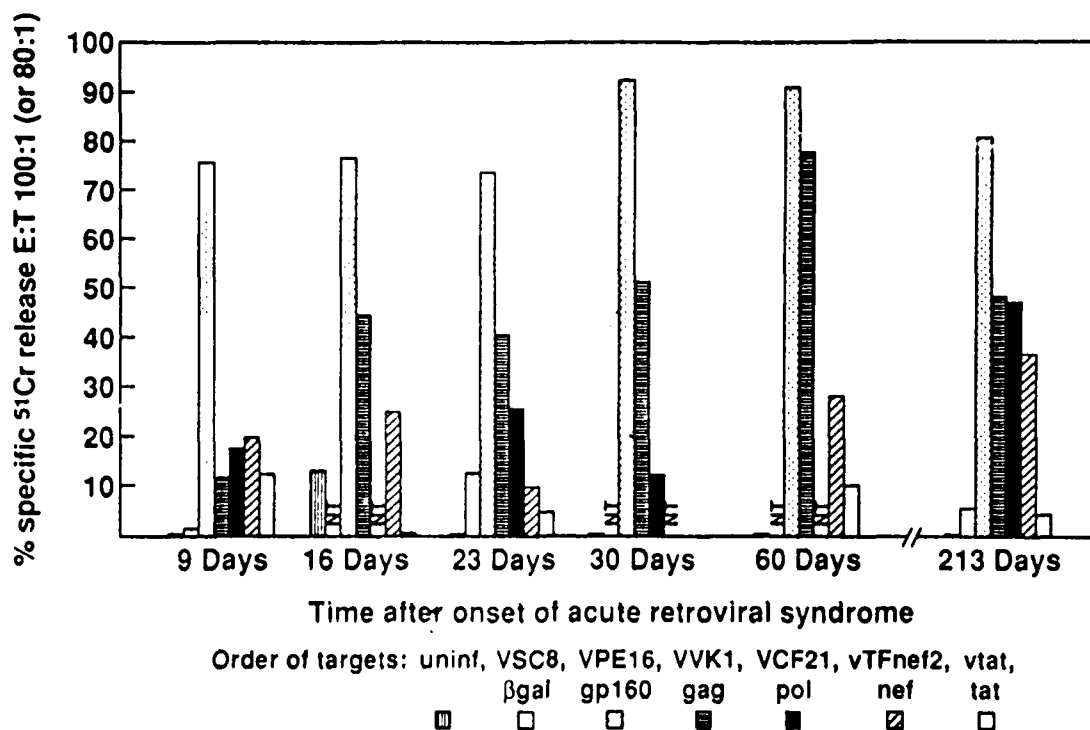
Figure 6

Longitudinal analyses of CTL activity for BORI and WEAU are near completion while data for SUMA and INME is partially completed and ongoing.

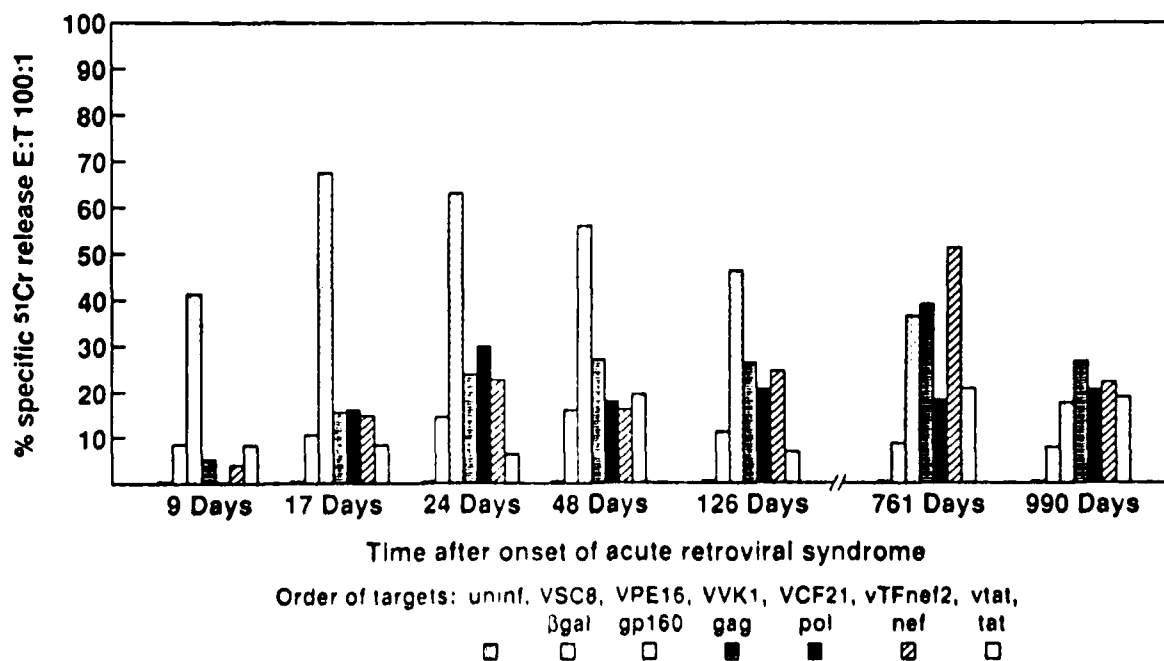
For Figures 7 & 8 -- See next page

**Figures 7 & 8** show CTL kinetics during the course of infection from BORI (Figure 7) and WEAU (Figure 8). Compare these responses to changes in viral load and viral clearance on same patients reported by Dr. Shaw's group (Piatak *et al.*, *Science* 259:1749-1754, 1993). These two patients are of interest because of decrease in CTL activity, increased viral load, and the development of disease (WEAU), or lack of decrease in CTL activity (BORI). Also note the highest CTL response is to ENV, not GAG, as frequently stated in the literature.

# LONGITUDINAL ANALYSIS OF THE CTL RESPONSE IN BORI



# LONGITUDINAL ANALYSIS OF THE CTL RESPONSE IN WEAU



Figures 7 & 8

Oldstone, Michael B. A.

CTL ENV epitope for BORI (HLA B-14 restricted) has been mapped and is located in gp120.

Table 2

Peptide used to coat targets	E.T. Ratio:	% Specific <sup>51</sup> Chromium Released from					
		BORI B Lymphocytes			Allo B Lymphocytes		
		50:1	25:1	12.5:1	50:1	25:1	
AVERYLKDQQL		46	41	33	7	6	
ERYLKDQQL		55	54	42	12	10	
<u>Vaccinia virus expressing</u>							
gp160		74	72	69	16	14	
gp120		27	51	49	5	2	
beta galactosidase		2	2	1	2	2	

ENV gene from BORI and WEAU is currently being manipulated to produce minigenes that express 110-120aa. These minigenes are being inserted into transfer vectors and then recombined with vaccinia virus. These reagents will be used in the future to map all the ENV epitopes.

Similar GAG minigenes expressing 350 to 400 amino acids have now been successfully placed in a shuttle vector and will be recombined with vaccinia.

### III. Summary of the Final Scientific Report

Three monoclonal antibodies to gp41 aa644-663 occurring in three HIV-1<sup>+</sup> individuals bind to a novel astrocytic antigen found in mammalian brains. An astrocyte gene encoding this novel antigen was not obtained. Astrocytes were noted to be the major (only?) source of tissue factor (TF) in the CNS. Further, TF mRNA which is constitutively expressed was noted to be markedly enhanced in certain persistent viral infections. CTL activity was kinetically followed in four selected patients from the early onset of infection over their clinical course. CTL activity to ENV occurs early and associates with the initial clearance of virus. The association of CTL activity late in disease when clinical AIDS occurs and the presence or absence of how CTL escape HIV variants is under current analysis. Three CTL epitopes for HIV were uncovered. One in this report and the two others are noted in the Mid-Term Report.

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#### **RESULTING GRADUATE DEGREES**

Michael Eddleston expects to receive his graduate degree in 1994